NEUROTENSIN AS A MODULATOR OF ALTERED CHOLINERGIC FUNCTION IN THE BRAIN, W. Rowe*, P. Lapchak, D. Araujo, A. Beaudet and R. Quirion, Departments of Psychiatry, Neurology and Neurosurgery, Douglas Hospital, Res. Center, McGill University, Montreal, Canada, H4H 1R3

Cognitive deficits are often associated with an impairment of cholinergic function. However, functional changes in the activity of other neurotransmitter systems such as neurotensin (NT) may also underlie certain cognitive behaviors most likely, via its actions on the cholinergic system. The distributional profile of NT and acetylcholine (Ach) in the rat and human brain suggest that a great deal of anatomical overlap exists between these two neurotransmitter systems. Acetylcholinesterase-positive neurons are in register with NT receptors in both rat and man. Alterations in NT receptor density have been reported to be associated with the amnesia produced by lesions of basal forebrain neurons (Wenk et al., 1989, Behav. Neurosci., 103: 765-769). Thus, it would appear that NT may interact with certain cholinergic projections, either directly or indirectly to regulate its activity.

NT, at doses as high as 10 μM, had no effect on basal acetylcholine (Ach) release in rat striatal slices. However, it potentiated in a concentration-dependent manner, K^+-evoked Ach release. NT also modulated Ach release in both the frontal and parietal cortices suggesting a functional involvement with the cholinergic system in these regions as well. Further, these NT-induced effects in the cortical areas were abolished by prior lesioning of the basal forebrain cholinergic neurons.

The functional significance of a NT/cholinergic interaction may relate to the emergence of cognitive deficits in our population of aged (24 month old) Long-Evans rats. We have previously shown that aged cognitively impaired (AI) rats display decreases in cholinergic function as compared with our aged unimpaired (AU) and young (CTL) animals. Significant decreases in Ach levels and altered muscarinic M2 binding sites were found in both hippocampal and cortical areas of the AI animal. This correlated with decreases in [^{125}I]NT binding in the hippocampal formation, entorhinal cortex as well as the septum and hypothalamus in the AI animal. Alterations in [^{125}I]NT binding sites in the AI animals suggest the possible involvement of the NT-ergic system in the age-related cognitive deficits seen in this animal. The fact that changes in NT receptor density occurs in parallel with alterations in cholinergic activity in the AI animal suggests a possible interaction between these two systems in mediating this effect. This research is supported by a grant from the Medical Research Council of Canada.